Benefits and challenges in using sero-prevalence data to inform models for measles and rubella elimination

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We use simulations to highlight how, accounting for the dynamical context, high-quality measles and rubella serological surveys can be used to inform key control and elimination questions if the challenges of conducting, analyzing, and interpreting them are overcome.

Abstract

Control efforts for measles and rubella are intensifying globally. It becomes increasingly important to identify and reach remaining susceptible populations as elimination is approached. Serological surveys for measles and rubella can potentially measure susceptibility directly, but their use remains rare. Here, using simulations, we outline key subtleties in interpretation associated with the dynamic context of age-specific immunity, highlighting how the patterns of immunity predicted from disease surveillance and vaccination coverage data may be misleading. High quality representative sero-surveys could provide a more accurate assessment of immunity if challenges of conducting, analyzing, and interpreting them are overcome. We frame the core disease control and elimination questions that could be addressed by improved serological tools, discussing challenges and suggesting approaches to increase the feasibility and sustainability of the tool. Accounting for the dynamical context, sero-surveys could play a key role in efforts to achieve and sustain elimination.

Keywords

serology; serological survey; measles; rubella; mathematical models; elimination

Introduction

Infectious diseases can persist in populations if there are enough individuals susceptible to infection to acquire and transmit infection. Infection from fully immunizing pathogens, such as measles and rubella viruses, leads to lifelong immunity, thus depleting the number of susceptible individuals in a population. Pathogen persistence is, therefore, only possible if susceptible individuals are replenished via births and immigration of susceptible persons. Measles and rubella vaccines are highly effective, reducing the rate of accumulation of susceptible individuals. These vaccines provide indirect protection to susceptible individuals by reducing the probability of effective contact between infectious and susceptible individuals, in addition to direct protection of immunized individuals. As a result, successful immunization programs can curtail or eliminate pathogen transmission [1]. Importantly, a small proportion of individuals fail to develop a long-lasting immune response after vaccination [2, 3]: we thus refer to 'vaccination' as the administration of vaccine and 'immunization' as the induction of a protective immune response via vaccination.

High measles vaccination coverage worldwide has reduced measles incidence and mortality to low levels in most countries, although progress in achieving high coverage with the first dose of measles-containing vaccines (MCV) has slowed recently [4]. While MCV has been in widespread global use for over 40 years, rubella-containing vaccines (RCV) have only recently been introduced into low income countries [5]. The World Health Organization (WHO) Region of the Americas was certified as achieving elimination of endemic rubella and measles in 2015 and 2016, respectively [6]. The remaining five WHO regions have measles elimination targets and three have set rubella control or elimination targets for 2020 [5]. Elimination efforts include attaining and sustaining high coverage with the first dose of MCV, scaling up of routine vaccination with a second dose of MCV, introduction of RCV, and supplemental

immunization activities (SIAs or campaigns) of both MCV and RCV [5].

Mathematical models indicate that elimination requires the achievement of a threshold level of population immunity (i.e., the percent of the population immune). This threshold differs between measles and rubella and between settings, but is determined by the pathogens' transmission potential [1] and the birth rate [7]. Elimination must be maintained by sustaining this level of population immunity through immunization or preventing re-introduction of the virus. The WHO recommends that programs use good quality data to monitor population immunity by identifying and responding to large numbers of susceptible individuals [8].

While analytic techniques can be used to infer population immunity profiles from vaccination coverage [9] and incidence data [10], these methods necessarily rely on indirect inference of immunity rather than direct measurement. Vaccination coverage data are often of poor quality [11] and can misrepresent population immunity because most countries lack data on vaccine effectiveness under field conditions and, assuming an average vaccine effectiveness, may over estimate population immunity in countries with weak cold chain systems. Further, where multiple doses are offered (e.g. a routine second dose or SIAs), doses may be disproportionately delivered to individuals who received a first dose [12]. Disease surveillance data may be biased due to non-specific diagnosis, preferential reporting of disease in young children, and gross under-reporting (e.g., in 2016, WHO estimated nearly 7 million (95% CI: 4.2 – 28.7 million) global cases [4], but only 132,137 were reported to the WHO [13]). For rubella, reporting is even less sensitive because surveillance was introduced recently, and 20 - 50% of rubella cases are sub-clinical or asymptomatic [14].

Serology can provide a direct measure of population immunity. Following infection or immunization, pathogen-specific immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies are produced. IgM antibodies persist for a few weeks while IgG antibodies persist for years to decades, although levels may decline over time. Measles virus-specific and rubella virus-specific IgG antibodies are recognized correlates of immunity, and antibody concentrations in the blood exceeding a threshold are deemed protective against infection or disease [15, 16]. Thus, in principle, high quality serological surveys, i.e., cross-sectional household surveys in which these antibodies are measured, allow direct measurement of a population's immunological profile. Depending on their design, serological surveys can reveal 'immunity gaps' (i.e., age groups or spatial locations where immunity is lower than expected, or below some operational threshold) thus identifying areas for additional vaccination efforts [17].

Because natural and vaccine-derived immunity cannot be distinguished, interpreting serological data requires accounting for historical changes in disease incidence and vaccination coverage (achieved both through routine services and SIAs), as we illustrate in this paper. We first delineate expectations for age-specific immunity profiles across a spectrum from endemicity to elimination. We describe how inferring immunity profiles from vaccination coverage data and/or reported case data (the current method used by most countries) can result in biases, showing the potential added value of serology. We then describe how serology could contribute to addressing two key questions for the control and elimination of measles and rubella**:** i) What are the most effective vaccination strategies to control and eliminate infection? And ii) how effective are current vaccination programs? We conclude by discussing challenges of serological surveys, providing suggestions for improving their feasibility and sustainability.

I. Age-specific serological profiles: expectations across a transmission spectrum from endemic to elimination.

Seropositivity in young infants results from the transplacental transfer of maternal IgG antibodies to the fetus. Antibody levels then decay exponentially as the infant ages. The proportion of seropositive children then increases at a rate determined by the rate of immunization through vaccination or infection. Age-specific sero-prevalence profiles vary over time as vaccine coverage and infection transmission vary, described below and illustrated in Figures 1 and 2 (model assumptions described in Tables 1 and 2, methods in Supplement S1).

a. Age-specific serological profiles in endemic settings

Where vaccination coverage is low or absent, the age-specific serological profile is largely dominated by natural immunity (Figure 1A). The rate of acquisition of immunity with age (following loss of maternal immunity) is determined by the rate of transmission in the population. If transmission is low, acquisition of infection and thus immunity is slow. Susceptible individuals may not encounter an infected individual until adolescence or older. R_0, the basic reproductive number representing the number of new infections per infectious individual in a completely susceptible population, is a commonly used measure of transmission potential that informs expected age-specific patterns of seropositivity [1]. Data detailing changes in the number of cases over time [10] or their distribution across ages [18], can be combined with mathematical models to estimate R_0 and infer expected age-specific immunity patterns. Additionally, the profile of cases accumulated across age strata may be used to reflect the cumulative proportion of immune individuals by age, although biases may emerge due to age-specific sensitivity of reporting.

Insensitivity of disease surveillance data can affect estimation of immunity gaps. Assuming optimistically that 5%-15% of cases are reported across a spectrum from endemicity to elimination (Table 2), Figure 2A

illustrates how using case data to estimate the fraction of the population naturally immune over age, *r(a)* (Figure 2A2), results in biased estimates of the proportion seropositive by age, *p(a)* (Figure 2A3), in an endemic setting. Poor quality of reported vaccination coverage further complicates interpretation of case data for understanding age profiles of immunity. Countries without national rubella vaccination programs often have low-levels of private healthcare sector vaccination [19] (Table 1). If unreported, this could bias estimates related to measures of transmission (e.g., R_0) and age-specific sero-prevalence profiles (Figures 2A1, 2A3); see Supplement S2 for an empirical example.

b. Age-specific serological profiles in settings with increased vaccine coverage

Where vaccination programs are well established, vaccine-derived immunity dominates the age-specific serological profile at younger ages. Older cohorts may have acquired natural immunity before high vaccination coverage was achieved, and maternal and natural immunity will continue to play some role.

Different strategies for vaccine administration (i.e., routine vaccination or SIAs) mean that the history of vaccine delivery can result in distinct age-specific sero-prevalence profiles (Figure 1, B-D). In low-income countries, routine MCV was designed to reach children during the first year of life. More recently children have access to a second dose of MCV, commonly in the second year of life [8]. SIAs are conducted periodically (usually every 2-5 years) over brief timeframes (usually days/weeks although potentially months/years in large countries) at the national or subnational level, and target specific age groups (e.g., 9 months-5 years of age). Outbreak response campaigns also occur. Information on the history of routine and SIAs allow inference into the age profile of vaccine-derived immunity, but data on vaccination coverage are often inaccurate [7, 11, 12]. Without individual vaccine histories, combining SIA coverage [20], outbreak response campaigns [21], and (where they exist) routine second dose programs may over-estimate susceptibility reduction, as vaccination may be disproportionately delivered

to immune individuals. For example, one study estimated that 31% of eligible populations were never accessible by routine or campaign vaccination in Sierra Leone [12]. Even if vaccine coverage were known precisely, not everyone develops protective immunity following vaccination [2] and vaccine-induced antibody levels may wane below the threshold for seropositivity [3] resulting in discrepancies between vaccination history and age-specific sero-prevalence.

Uncertainties in vaccination coverage data combined with underreported incidence (Table 2) result in errors in estimates of the proportion seropositive by age (Figure 2, B-D). Estimated vaccination coverage is likely to overestimate the proportion immunized, *v(a)* (Figure 2, B1 C1 D1), even after accounting for vaccine failure. Incomplete surveillance biases estimates of the proportion immune from natural infection, *r(a)* (Figure 2, B2 C2 D2), furthering biasing inferred seropositivity, *p(a)* (Figure 2, B3 C3 D3). Improving case surveillance reduces the degree of bias (Figure 2).

Immunity derived from natural infection remains a source of seropositivity in expanded control settings, but an erratic, potentially misleading one. For example, extended periods of low incidence following vaccine introduction may allow accumulation of susceptible individuals [1]. Eventually, their proportion may grow sufficiently large to sustain an outbreak. Incidence thus provides a poor indicator of population immune status: low case numbers can reflect either sustained, high levels of population immunity or an increasing risk of an outbreak. Imperfect surveillance combined with uncertainty in vaccination coverage data further complicate estimates of age-specific population immunity.

c. Age-specific serological profiles in near elimination settings

As elimination approaches, the prevalence of immunity derived from natural infection decreases and vaccine-derived immunity increases. Reconstructing immunity profiles without serology is complicated

by vaccination coverage uncertainty, absent or rare case data from surveillance, and the resultant decline in positive predictive value of cases reported [22], unless all cases are laboratory-confirmed. Estimating the age-specific immunological profile is important to identifying vaccination age targets to achieve and sustain elimination. One particular near-elimination setting issue relates to maternally derived immunity. Given that maternal antibodies neutralize vaccine virus, vaccine efficacy increases with age as maternal antibodies wane (Figure 3A). Accordingly, administration of the first dose of MCV is usually delayed until 9 or 12-15 months of age to ensure infants are free of maternal antibodies. However, vaccinated mothers transfer a lower level of measles virus-specific antibodies to their children than naturally-infected mothers [23], potentially leaving these children susceptible to measles at an earlier age, and raising questions about shifting the age of vaccination younger (see below). Robustly characterizing such nuanced patterns without serology is challenging.

II. Addressing key questions for the control and elimination of measles and rubella

a. Strategizing effective targeting of vaccination to control and eliminate infection

In mature vaccination programs, additional efforts would ideally target immunity gaps that could allow outbreaks [8]. Populations are at risk of an outbreak when the number (density) of susceptible individuals is sufficiently large. Susceptible individuals are distributed over age (and space, see Supplement S3). Age-specific sero-prevalence estimates, combined with data on mixing-patterns by age and vaccination coverage, can help estimate susceptibility and characterize outbreak risk [7, 24], thus helping program managers prioritize strategies to close immunity gaps.

One way to tackle immunity gaps is by *modifications to the timing and targeting of vaccination campaigns*. For example, low seropositivity in age classes thought to be important for transmission, e.g.,

school children, suggest a need to increase vaccination coverage in this age group (assuming a sensitive laboratory assay and appropriate seropositivity cut-off have been used [25], as antibody levels wane after vaccination especially in the absence of boosting from exposure to wild-type virus [15, 16]). For example, observing low immunity in children aged 7-10 years (Figure 1B) before a planned vaccination campaign strongly supports extending the age range of the campaign beyond age 5 years to close this immunity gap.

Serological data could also be used to *help determine the need for a vaccination campaign*. Sero-surveillance is conducted in high-income countries such as Japan [26], Australia [27], the United Kingdom and the Netherlands [28], and has contributed to vaccine policy recommendations such as initiating catch-up campaigns [29, 30]. A sero-surveillance system that triggers vaccination campaigns may be particularly valuable in near-elimination settings since sparse case data is a poor indicator of increases in population susceptibility and immunity gaps may go undetected until an outbreak occurs [31]. Historically, these outbreaks have had age distributions that deviate from expected patterns of age susceptibility based on historical vaccination coverage data (e.g., Malawi [21]). Sero-surveys can reveal changes in the age distribution of immunity, providing an opportunity to conduct campaigns to fill immunity gaps before outbreaks occur [32]. Importantly, survey results must be available promptly, so that vaccination campaigns can be planned and implemented rapidly in response to serological data.

One additional benefit of age-specific sero-prevalence is the potential to *fine-tune age of routine vaccination* in high vaccine settings. The ideal age of the first dose of MCV will optimize vaccine effectiveness without increasing the number or severity of measles cases [33]. Although the WHO Americas Region successfully sustained measles elimination after an increase in the age for the first dose of measles vaccine [6], in other regions cases before the age of 9 months remain a concern. Because mothers with vaccine-induced immunity have lower antibody levels than those with infection-induced

immunity, babies born to the former have lower levels of maternal antibody and become susceptible at an earlier age. The transition to elimination could therefore result in more unprotected infants below the age of routine vaccination [23]. In the WHO African region, high birth rates mean that this could eventually translate to large numbers of susceptible individuals capable of maintaining measles virus transmission [34], an effect potentially amplified by high rates of HIV infection which reduces the efficiency of trans-placental transfer of maternal measles-specific antibodies [35]. As more countries have extended periods of low measles incidence and more women of child-bearing age have vaccine-induced immunity, the optimum age for routine administration of first and second doses of MCV becomes an important policy question, that serology could potentially inform. However, given the narrow age window affected, the programmatic scale of the interventions implied, and the scope of impact of any change, detailed data beyond cross-sectional age-serology (e.g., clinical trials) may be probably be required to inform policy decisions.

b. Evaluating the effectiveness of vaccination programs against infections

Serology can be used to assess the effectiveness of vaccination activities, impact on disease burden, and progress towards elimination.

The role of SIAs in achieving measles elimination is receiving increasing scrutiny because of the high costs and human resource needs required to successfully conduct campaigns. Sero-surveys have been suggested as one option to evaluate their success [17]. However, cross-sectional sero-surveys cannot currently distinguish immunity from natural infection from vaccine-induced immunity (Figure 2), complicating use of a single post-campaign sero-survey to evaluate SIA impact (although detection of IgM antibodies within weeks of an SIA may indicate immunization of a susceptible individual, as individuals with prior immunity should not mount an IgM response). Conducting pre- and post-campaign

serological surveys does allow measurement in the increase in immunity due to the SIA, demonstrated in England and Wales [30], Australia [36], and research settings in Ethiopia [37] and Kenya [38].

If a pre-campaign sero-survey is not feasible, sero-surveys can determine whether target immunity prevalence has been reached, without drawing specific conclusions about the vaccination campaign. Otherwise, nuanced inferential tools combining data from sero-surveys with age-specific disease incidence and the history of vaccination can estimate vaccination campaign effectiveness, although uncertainties with these data sources (see above), remain a limitation.

Age-specific serological data are also a valuable resource to indirectly infer disease burden. The burden of congenital rubella syndrome (CRS) is difficult to measure directly, given complexity of diagnosis and difficulty of reporting in settings with limited medical resources [39]. Estimates obtained by combining the age-specific force of infection derived from age-specific serological data with the age-profile of fertility, and risk during pregnancy provide the only estimate of CRS in many countries [40] (see Figure 3B).

Finally, serological surveys provide an additional source of population immunity estimates, a necessary line of evidence for measuring progress towards and verifying elimination [41, 42]. The WHO Americas Region success in eliminating measles and rubella largely without reliance on serological data to inform vaccination policy is likely to have been the outcome of the robustness and consistency of their vaccination programs. Other WHO regions may require broader data streams to describe their unique transmission dynamics. In African countries, vaccination coverage varies substantially within and between countries [43] and data on SIA coverage are suboptimal, especially regarding their effectiveness in reaching previously unimmunized persons [12]. Vaccine refusal in European countries, and

increasingly elsewhere, can result in patches of susceptible individuals associated with considerable outbreak risk, given high importation rates of infected individuals due to inter- and intra-migrations [44]. Sero-prevalence profiles are correspondingly hard to anticipate [7, 21].

III. Serological survey challenges

High quality, cross-sectional household serological surveys with blood specimen collection require: i) substantial financial resources and time commitment, ii) logistical capacity and skilled personnel to design and conduct a sero-survey that is generalizable to the target population, iii) laboratories and laboratory expertise to perform serological assays with quality control and assurance, and iv) expertise in statistical analysis to interpret serological data [17]. Sero-surveys are thus typically not prioritized in low- or lower-middle income countries, but there is potential to make them more feasible and sustainable by: i) expanding capacities in conducting high quality household surveys such as vaccination coverage surveys [11], ii) including serology in vaccination coverage and/or multi-purpose household surveys (as already is done for HIV [45]), iii) expanding existing sentinel site surveillance systems to include measles/rubella serology, iv) expanding the scope of serological surveillance to other vaccine preventable and emerging infectious diseases (e.g., multiplex assays), and v) standardizing specimen collection, testing, and interpretation of serological results (see Supplement S4 for further discussion).

The WHO is rolling out updated guidance for the conduct of high quality vaccination coverage surveys [46]. Established household survey programs such as the Demographic and Health Surveys offer opportunities for inclusion of serology in many countries. Major barriers remain, however, including

difficulty in ensuring high participation rates, especially for invasive samples (e.g., blood, which often has the benefit of reduced laboratory uncertainty) [47], difficulty in standardizing different laboratory assays [47, 48], and challenges in defining appropriate cut-offs for seropositivity [48] (although expanded deployment of statistical methods such as mixture models could formally address individual variability in cut-offs [49]).

For measles, a cut-off of 120 IU/L is proposed as indicating protection from infection, from plaque reduction neutralization assay results on blood samples obtained before and after a measles outbreak in American college students [50]. This cut-off may not be appropriate (a) if less sensitive, non-functional assays such as EIA are used [47] and (b) when seeking evidence of past immunization (in which case a lower threshold may be appropriate) irrespective of whether antibody levels have persisted above the putative fully protective threshold. Likewise, for rubella, antibody levels wane after vaccination and EIAs lead to a high number of false negative results [48]. Careful examination of the data can lead to more appropriate cut-off choice, aligned to the survey objectives, rather than using universal cut-offs (e.g., 120 IU/L for measles; 10-15 IU/ml for rubella). Much remains to be done to identify, or develop, field-friendly assays that consistently provide readily interpretable data from surveys in low- and middle-income countries [17, 25].

Conclusions

As countries approach measles and rubella elimination goals, the age profile of immunity, and the relative contribution of natural and vaccine derived immunity change. High quality sero-surveys allow explicit characterization of the distribution of immunity at a particular time-point, but also an opportunity to evaluate assumptions made about natural transmission dynamics and vaccine program performance. However, given the costs and challenges inherent in deploying serological surveys, the potential gain in

inference should be considered carefully before such surveys are planned. Dynamic models can link serology, clinical, and programmatic surveillance to generate robust estimates of the profile of immunity. Immunity gaps identified through multiple data sources, including serology, can be used to target specific interventions and improve routine programs to prevent future gaps. Finally, investment in sero-surveillance for the goal of measles and rubella surveillance could form the foundation of broader sero-surveillance efforts as multiplex assays become increasingly available.

Table 1: Assumed routine and SIA vaccination coverage over time in the simulated population displayed in Figure 1. The first 10 years of low vaccination coverage represent an example of RCV administered in the private-sector only [19]. Increased routine vaccination at 10 and 20 years represents introduction of RCV into national vaccine schedules, and then expansion of the programs to capture more infants, respectively. SIAs at 10 and 18 years represent typical SIA efforts to vaccinate many young age groups. **(**mo = months old, yo= years old)

Year	Routine coverage (age range)	SIA coverage (age range)
0	~10% (9mo - 12mo)	
1	~10% (9mo - 12mo)	
2	~10% (9mo - 12mo)	
3	~10% (9mo - 12mo)	
4	~10% (9mo - 12mo)	
5	~10% (9mo - 12mo)	
6	~10% (9mo - 12mo)	
7	~10% (9mo - 12mo)	
8	~10% (9mo - 12mo)	
9	~10% (9mo - 12mo)	
10	~50% (9mo - 12mo)	70% (1yo - 5yo)
11	~50% (9mo - 12mo)	
12	~50% (9mo - 12mo)	
13	~50% (9mo - 12mo)	
14	~50% (9mo - 12mo)	
15	~50% (9mo - 12mo)	
16	~50% (9mo - 12mo)	
17	~50% (9mo - 12mo)	
18	~50% (9mo - 12mo)	80% (1yo - 5yo)
19	~50% (9mo - 12mo)	
20	~90% (9mo - 12mo)	
21	~90% (9mo - 12mo)	
22	~90% (9mo - 12mo)	
23	~90% (9mo - 12mo)	
24	~90% (9mo - 12mo)	
25	~90% (9mo - 12mo)	
26	~90% (9mo - 12mo)	
27	~90% (9mo - 12mo)	
28	~90% (9mo - 12mo)	
29	~90% (9mo - 12mo)	

Table 2: Assumed data error assumptions used to infer estimates of proportion immune (vaccine-induced, natural infection-induced, and total) in Figure 2. We assume vaccination coverage, when available, is biased upwards [11] conservatively by ~10% [12], and reporting starts relatively low, improving as vaccine coverage improves. Given biased coverage estimates, knowledge of the age targets, timing of SIAs, and age-specific vaccine effectiveness, the age profile of vaccine-induced immunity, $\widehat{v(a)}$ was re-constructed. Given biased incidence data, the proportion immune by natural infection, $\widehat{r(a)}$, was estimated adjusting for under-reporting (assuming 85% underreporting). These two (biased) estimates allow estimation of total proportion immune, $\widehat{p(a)}$, by age assuming independence between the two sources of immunity, i.e., $\widehat{p(a)} = 1 - ((1 - \widehat{r(a)})(1 - \widehat{v(a)}))$.

Time point	vaccination coverage data error assumptions	incidence data error assumptions
6	unavailable	under-reported by 95%
11	over-reported ~10%	under-reported by 92%
16	over-reported ~10%	under-reported by 88%
26	over-reported ~10%	under-reported by 85%

Figure Legends

Figure 1: A simulated population from a rubella transmission model (see Supplement S1 for model details). **Top panel** displays the time-series of incidence of infection in a changing context of increased vaccination coverage (see Table 1). **Bottom panels A-D** display age profiles of immunity after 6, 11, 16, 26 years, respectively; dashed red vertical lines indicate age ranges affected by the SIAs in preceding years. Bottom panel shows: A) Proportion immune under low vaccination coverage results in a gradual increase over age after the decay of maternal immunity. B) Increased routine vaccination to 50% slows the rate of acquisition of immunity through natural infection, but vaccine-acquired immunity increases at rates reflecting routine vaccination delivery and SIAs, resulting in further age-specific increases in targeted age groups (affecting 2-7 year olds here). C) During periods of control, immunity in relevant age-classes reflects routine vaccination coverage in ages 1 to 6 years, corresponding to low incidence between year 10 and year 13 (see incidence time-series). In year 15, a resurgence affects individuals just outside the target age group of the 1st SIA, i.e., individuals >age 6 in year 10, and >age 12 in year 16. D) Erratic age-specific immunity profiles emerge under increased routine coverage: while immunity in ages 1-6 closely reflect the 90% vaccination coverage, the dip in 8 year olds occurs because the 2nd SIA reduced incidence, and therefore these children had a low risk of natural infection but were too young to be immunized during the 2nd SIA, or the increase in routine coverage that occurred in year 20.

Figure 2: Comparison of inferred age-specific immunity from inaccurate coverage and case surveillance data to 'true' age-specific immunity using a simulated population. Right panel displays time-series of incidence in a changing context of increased vaccination coverage (see top panel Figure 1). **Left panels A1-D3** display age-specific proportion vaccinated (v(a); A1, B1, C1, D1), proportion recovered from natural infection (r(a); A2, B2, C2, D2), and proportion immune (p(a); A3, B3, C3, D3) at years 6, 11, 16, 26, respectively. Blue lines represent the 'truth' and black dashed lines represent the inferred age-trajectories, assuming some error in vaccination and incidence data (see Table 2 for data error assumptions). False positives from estimated v(a) and false negatives from estimated r(a) both contribute to the error in estimated p(a). The added value of a high-quality representative IgG serological data (assuming minimal diagnostic testing error) is clear as uncertainties associated with vaccination coverage and incident case data greatly bias estimates of age-specific immunity.

Figure 3: Example serological survey data. A) Measles IgG titers for a representative sample of the Netherlands [23]; infants with maternally-derived antibodies in blue (main plot and inset); threshold for protection (immunity) shown by the horizontal dashed line. By contrast with categorical data (positive versus negative, see previous figures), this quantitative measure reveals the distribution of antibody concentrations relative to the threshold of protection, and can be used to study maternal antibody

decay (see main text). **B)** Fraction of individuals seropositive from rubella antibodies in urban and rural Vellore, India [40]. Associated estimates of the magnitude of transmission can be combined with age fertility to infer the burden of CRS pre-vaccination. For this example, assuming that age-specific contact patterns and private-sector vaccination coverage were comparable in both settings, these patterns suggest higher transmission in urban than rural settings, as the increase in age-specific sero-prevalence is faster in urban settings. Accounting for differences in fertility, higher transmission of rubella in urban Vellore contributed to lower estimated risk of CRS compared to rural Vellore [40].

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